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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,193	10/23/2001	Qinghong Yang	10752-005-999	7211

24341 7590 03/25/2003

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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,193	YANG ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10/01; 7/03; 9/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities. It is noted that Applicant filed substitute drawings on April 19, 2002. The substitute drawings include a figure identified as "Figure 2" that depicts "Table 1." However, the "Brief Description of the Drawings" in the specification describes only Figures 1A and 1B. Accordingly, amendment of the specification to include a description of "Figure 2" is required (see *MPEP* 608.01(f) and 37 CFR 1.74). Further, as "Table 1" has now been provided in Figure 2, the version of the Table appearing at the end of the specification, and the description thereof at page 4 of the specification, should be deleted.

Appropriate correction is required.

2. The use of the trademarks Taq Gold™ and PicoGreen® has been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Information Disclosure Statement

3. The information disclosure statement filed October 23, 2001 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in

the English language. As English language abstracts were provided for documents AJ and AK, the English abstracts have been considered, and the notation "English abstract only" has been added to the signed and initialed 1449.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 are indefinite over the recitation of the phrase "detecting or quantitating the release of the probe polynucleotide or release of a strand of the reference polynucleotide from the solid support as a n [sic] indication of the genotype of the target nucleic acid" in claim 1, step d. First, there is insufficient antecedent basis in the claims for the limitations "the reference polynucleotide" and "the target nucleic acid;" claim 1 previously refers to a "target polynucleotide" and a "reference nucleic acid," but not to a "reference polynucleotide" or a "target nucleic acid." Second, while it is clear that step d requires one to detect and/or quantitate the release of a nucleic acid molecule, the claim as written does not make clear how detection/quantitation of release of a molecule actually allows one to determine the genotype of the target polynucleotide. For example, what genotype is "indicated" if probe is released and/or if "a strand of the reference polynucleotide" is released (and would the release of these molecules indicate the same or different genotypes?)? Further, if neither molecule is

released, is genotype still determined (and if so, what genotype?)? As the claims are drawn to a method "for determining the genotype" of a target polynucleotide, clarification is required such that one of skill in the art would be apprised as to how the performance of the method steps of the claims results in this objective. It is also noted that while it is clear that the recitation "a n" is intended to recite "an," it is suggested that applicant amend the claim to correct the typographical error.

Claim 2 is indefinite over the recitation of the limitation "said nucleic acid sequences" because there is insufficient antecedent basis for this limitation in the claims. Claim 1 does not recite the term "nucleic acid sequences."

Claims 4-5 are indefinite over the recitation of the limitations "wherein the probe polynucleotide can be detectably labeled" in claim 4 and "wherein at least one strand of the reference nucleic acid can be detectably labeled" in claim 5. As it is a property of any polynucleotide or nucleic acid that it "can be detectably labeled," it is unclear as to how or whether these recitations further limit the claimed invention. It is also unclear as to whether these recitations are intended to somehow modify or limit, e.g., the structural and/or functional properties of the "probe polynucleotide" and the "reference nucleic acid," or whether this recitation may be intended to, e.g., refer to a step of labeling that may be included in the claimed method, or to a labeling that may occur as a result of strand exchange during the practice of the method. It is noted that if Applicants' intent was merely to indicate that the molecules employed in the method may be labeled or unlabeled, this rejection could be overcome by amending the claims to recite, e.g.,

"wherein the probe polynucleotide is selected from an unlabeled probe polynucleotide and a detectably labeled probe polynucleotide."

Regarding the recitation of the term "the reference polynucleotide" in claim 6, it is noted that while claim 1, step d, recites the term "the reference polynucleotide," antecedent basis for this term is lacking in claim 1, as discussed above. Accordingly, both claim 1, step d, and claim 6 should be amended so as to recite a limitation for which antecedent basis is provided (e.g., to recite "the reference nucleic acid").

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lishanski et al (WO 97/23646 A1 [published 7/1997]) in view of Abrams et al (US 6,238,927 B1 [5/2001; filed 10/1999]).

It is first noted that specification discloses that the target polynucleotide of the invention is immobilized on a solid support that "can comprise any material known to those of skill in the art on which a polynucleotide can be immobilized," and that the specification specifically teaches beads as an example of a solid support that may be employed in the invention (see page 10, lines 21-31, particularly lines 23-24 and 26).

Lishanski et al disclose methods for detecting target nucleic acids, methods for detecting mutations, and methods for detecting differences in related nucleic acid sequences (see entire reference). Lishanski et al's methods comprise steps of forming a partial duplex from a target nucleic acid and a complementary probe, contacting the partial duplex with a partial duplex that comprises a reference nucleic acid, and subjecting the two duplexes to conditions that allow them to hybridize with one another, wherein formation of a stable complex of the four strands (i.e., a "four way" complex) indicates the presence of a difference or mutation (see entire reference, particularly, e.g., page 5, lines 10-30; page 8, lines 21-41; page 19, line 35-page 20, line 10; see also page 4, lines 9-11, page 7, lines 6-8, and page 8, lines 35-37 regarding the presence of 4 strands in the complex formed during the practice of Lishanski et al's methods). Lishanski et al disclose that branch migration during their reaction conditions results in formation of stable complexes when a difference/mutation exists between the target partial duplex and the reference partial duplex, and completed strand exchange

(such that two new duplexes are produced) when a difference/mutation is absent (see, e.g., page 11, lines 1-5, page 13, lines 29-37; page 19, line 35-page 20, line 10). While Lishanski et al do not refer to "genotyping," Lishanski et al teach that their method is "universal and permits detection of any difference in two related nucleic acid sequences, whether or not such difference is known" (see page 10, lines 28-30). Further, Lishanski et al exemplify the differentiation of heterozygotes, "wild-type" allele homozygotes and "mutant" allele homozygotes of exons 10 and 11 of the CFTR gene (see page 39 and Examples 1-13). Lishanski et al thereby teach methods in which the genotype of the CFTR gene is determined, and it is a property of such methods that they constitute genotyping. Lishanski et al disclose attachment of complexes to a solid support to facilitate detection (see, e.g., page 27, lines 22-24) and disclose the use of target polynucleotides attached to solid supports such as beads to facilitate separation of complexes for detection (see, e.g., page 31, line 31-page 34, line 5). While Lishanski et al disclose that their methods comprise detection of mutations/differences by detecting labels in a complex, or by determining the presence of a complex in another manner (see, e.g., page 3, lines 37-39; page 7, lines 5-11; page 11, lines 3-5; page 30, line 37-page 34, line 5), Lishanski et al also disclose that the absence of a complex is indicative of complete strand exchange and formation of new duplexes (see, e.g., page 20, lines 8-10), and thereby disclose detecting the absence of a complex as an indicator of complete strand exchange and the absence of a difference/mutation. Further, in a embodiment of Lishanski et al's method in which the target polynucleotide is attached to a solid support such as a bead (as discussed above), the resolution of complexes to

form 2 new duplexes would necessarily result in a bead-attached duplex containing the target polynucleotide and one reference strand, and an unattached duplex containing the probe polynucleotide and the other reference strand. However, Lishanski et al do not actually disclose or exemplify detection or quantitation of the release of the probe polynucleotide or the release of a reference nucleic acid strand from a solid support as an indicator of genotype, as required by the instant claims.

Abrams et al disclose methods of detecting target nucleic acids in which detection is accomplished via the displacement of one strand of an immobilized duplex molecule by hybridization of either the immobilized or unattached strand of the duplex with another single stranded molecule followed by branch migration (see entire reference, particularly column 2, lines 48-67; column 6, lines 30-49; column 7, lines 43-56; Figures 1-2). Abrams et al teach that the use of a duplex containing one strand attached to a solid support facilitates separation and analysis of released duplexes (see, e.g., column 7, lines 47-52), and disclose that gel electrophoresis allows detection in the same gel of both the amount of the newly formed, released duplex and the amount of the remaining (original) immobilized duplex (see, e.g., Figure 3 and column 11, line 65-column 12, line 51, particularly column 12, lines 39-44).

In view of the teachings of Abrams et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lishanski et al so as to have employed in Lishanski et al's method of genotyping an immobilized target polynucleotide, and so as to have included in the method, in addition to the step of detecting complexes taught by Lishanski et al, a step

of gel electrophoresis to detect released probe/reference strand duplexes as an indicator of genotype. As discussed above, Lishanski et al's method includes a step of detecting the presence or absence of complexes, wherein the presence of complexes indicates that the genotype of the target nucleic acid differs from that of the reference nucleic acid, and wherein the absence of complexes indicates that the genotype of target and reference molecules are the same. However, as Lishanski et al's method lacks a step in which free duplexes are actually detected, one of ordinary skill in the art would have recognized that while the detection of the presence of complexes would clearly indicate a particular genotype, the absence of complexes could be indicative either of a different genotype or of a failure of the assay (e.g., failure of preliminary amplification such that sufficient target molecules are absent, failure to use appropriate buffer conditions such that hybridization cannot occur, etc.), such that the absence of complexes may be inconclusive and not in fact indicative of genotype. Thus, as the gel electrophoresis method step of Abrams et al allows for detection of both immobilized complexes and released molecules, an ordinary artisan would have been motivated to have added such a step to the method of Lishanski et al in order to have both confirmed that the assay functioned as intended and to have detected the presence of released duplexes as a conclusive indicator of genotype, for the advantage of increased accuracy in determining genotype. Regarding step d of the claimed method, it is further noted that the gel electrophoresis of Abrams et al results in determination of the relative quantities of different reaction products (see, e.g., Figure 3), and thereby results in a type of "quantitating" of released products.

Regarding claim 2, it is further noted Lishanski et al disclose the use of DNA in their methods (see, e.g., page 11, lines 11-28). Regarding claim 3, Lishanski et al disclose that the complex formed during the practice of their methods may comprise a Holliday junction (see, e.g., page 3, line 37; see also page 2, lines 9-16 and page 13, lines 29-33). Regarding claims 4-5, it is again noted that Lishanski et al disclose labeling of both probe and a reference nucleic acid strand (see, e.g., page 3, lines 33-37; page 5, lines 10-30; page 8, lines 21-41). Regarding claim 6, Abrams et al disclose detection of released molecules by gel electrophoresis, as discussed above.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
March 23, 2003